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An analysis of the spatial arrangement of the myocardial aggregates making up the wall of the left ventricle

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Abstract

Objective: We used the technique of peeling of myocardial aggregates, usually described as 'fibres', to determine the spatial arrangement of the myocytes in the left ventricular wall of a healthy autopsied human heart. **Methods:** We digitised the left ventricular outer and inner boundaries, as well as the pathways in space, of almost 3000 aggregates harvested from the left ventricular myocardium. During the process of gradual peeling, we sought to identify the myocardial aggregates as uniformly as possible. Despite this, interpolation was necessary to complete the pattern so as to construct a unit vector field that represented the preferred direction of the myocardial aggregates throughout the entirety of the walls of the left ventricle of this individual human heart. **Results:** Apart from the overall systematic arrangement of the aggregates necessary to achieve physiologic ventricular contraction, we documented substantial local heterogeneities in the orientation of the myocardial aggregates. In particular, a significant proportion of aggregates was found to intrude obliquely with respect to the ventricular boundaries, with markedly heterogeneous distribution. Moreover, the distribution of the helical angle of the aggregates relative to the ventricular base varied notably throughout the left ventricular free walls and the septum. Within the generally quite uniform and continuous structure of the ventricular mass, we were, however, unable to identify any organised tracts or functional subunits such as a 'helical ventricular band', nor did we find radial fibrous lamellas coursing across the ventricular wall. **Conclusion:** We suggest that the impact of local anatomical inhomogeneities, associated with gradients in regional contractile function on global ventricular dynamics, has been systematically underestimated in the past. Our analysis confirms furthermore the continuous nature of the myocardium associated with an overall gross organisation of the fibre direction field; however, there is no evidence of substructures compartmentalising the ventricles.

Keywords: Heart; Left ventricular architecture; Myocardial aggregates fiber orientation

1. Introduction

The cardiomyocytes making up the walls of the ventricles are aligned such as to ensure ejection of blood subsequent to their activation. To this end, the myocardial mass exhibits a systematic gross architecture along with a number of unique anatomical and physiologic properties that differ from other muscular tissues. The significance of these properties is emphasised by the fact that the myocardium may fail if the overall regular alignment is disturbed by myocytic disarray or fettered by fibrosis.

Anatomists have shown in numerous previous studies that the myocardium is arranged as anisotropic continuum, with the individual myocytes aligned in series and coupled to their neighbours through multiple offsprings, the overall mesh being supported by a matrix of connective tissue [1,2]. These earlier studies emphasized that, in contrast to skeletal muscle, the cardiac muscular pathways have no beginnings and endings. Rather, the highly branched myocardial architecture allows multiple, and virtually endless, continuations within the myocardial mesh at any location within the ventricular wall. A number of investigators have nevertheless sought to identify a further order of organisation within the ventricles, either using techniques of dissection [3] or on the basis of histology [4]. Evidence supporting the existence of such anatomical features is, however, lacking [5,6]. A particularly prominent concept relates to the existence of a 'helical myocardial band', which was used, among others, to formulate revisionist accounts of cardiac development, as well as propose the basis for new operative

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procedures [7]. Indeed, it has been suggested that the arrangement of the ventricular myocytes is akin to the architecture of ancient structures such as Stonehenge [8].

Although there is no evidence for compartmentation of the ventricular mass, we should note that several of the published anatomic studies have shown that the arrangement of the myocytic aggregates within the left ventricular walls is far from uniform [1,2,5]. Previous investigations have also shown that there are countless small planes of cleavage interspersed throughout the myocardium, which facilitate relative movement between adjacent myocardial aggregates, thus easing their rearrangement during systolic contraction and diastolic relaxation [4,8—12]. Histology has furthermore established that, despite the highly interlaced nature of the ventricular myocardium, there are numerous local heterogeneities in the orientation and connections of the myocardial aggregates making up the ventricular wall [5,6].

All of these aspects are key to ongoing debates amongst cardiodynamocists. In attempts to discern a common pattern within the wide variety of mammalian hearts, anatomical and mathematical models of the ventricles have mostly been based on idealised, and mostly uniform, geometric representations [13,14]. It has, in particular, been assumed by some of the modellers that the mural structure is homogeneous throughout the ventricle and that the influence of myocardial aggregates making up the ventricular walls which do not essentially run parallel to the surface can be neglected [14]. An exception is the model analysed by Bovendeerd et al. [13], where an axisymmetric geometry is considered, with a uniform population of obliquely intruding aggregates. Most models, however, depend on assumptions and simplifications made in order to arrive at a myocardial structure which is sufficiently uniform and systematic to permit mathematical analysis [14].

With all these problems in mind, our current aim was to use the technique of peeling to establish the alignment of the myocardial aggregates within the entire ventricular wall of a representative healthy human heart, taking into account local details and irregularities. We paid particular attention to the statistical distribution within the ventricular components of the so-called helical and intrusion angles, these being defined as the angle subtended by the aggregates relative to the ventricular base, and the angle between the aggregates and a plane tangential to the ventricle's outer surface, respectively. The results support the time-honoured notion that the myocardium possesses a systematic architecture, albeit with significant local heterogeneity, but without any evidence for a radial compartmentation of the ventricular walls. Although examining only a solitary heart, we submit that our findings are highly relevant to the ongoing debates concerning myocardial architecture [6,7].

2. Material and methods

A human heart without documented pathology, obtained 48 h after death, was first perfused for 12 h with saline to wash out blood from the coronary arteries. The heart was thereby suspended at the canula which was tightly fixed in the aortic root while being submerged in the perfusate with the atrial aperture open to the surrounding fluid. The perfusate was subsequently replaced by a 10% formaldehyde solution, and the perfusion was continued for 24 h. Perfusion pressure was measured to make sure that it did not exceed 120 mm mercury (ca. 16 kPa). The atrial walls were trimmed down to the ventricular base, and the heart was submerged for 2 weeks in 10% formaldehyde solution, the transmural pressure being zero. The ventricles were then filled with Technovit (Haereus-Kulzer, Germany) to provide mouldings of the ventricular cavities. Together with the two-component resin, a wooden rod was anchored axially in the left ventricular cavity, which served to fix the heart in a jig on top of an electromagnetic digitising tablet (3 Draw Digitizer System, 3 SD 005, Polhemus, Cochester VTO 5446, USA). The right ventricle was cut away [15].

After removal of the epicardium and the coronary arteries, together with their perivascular fat, we digitised the left ventricular outer surface. The location in space was determined and stored pointwise using an electromagnet system operating a stylus, its tip being recorded with the aid of a digitising tablet. At the end of the procedure of peeling, we digitized the revealed endocardial surface. We then derived closed surfaces from the point clouds, containing typically 2000 points representing the endocardial, and some 4500 points representing the outer surface (Raindrop Geomagic®), using a mathematical procedure based on Non-uniform Rational B-Splines (NURBs), which implied filtering in order to remove artefactual noise introduced by the manual outlining process (Fig. 1).

The aggregated myocytes were displayed in an anatomically systematic sequence, starting from the base of the

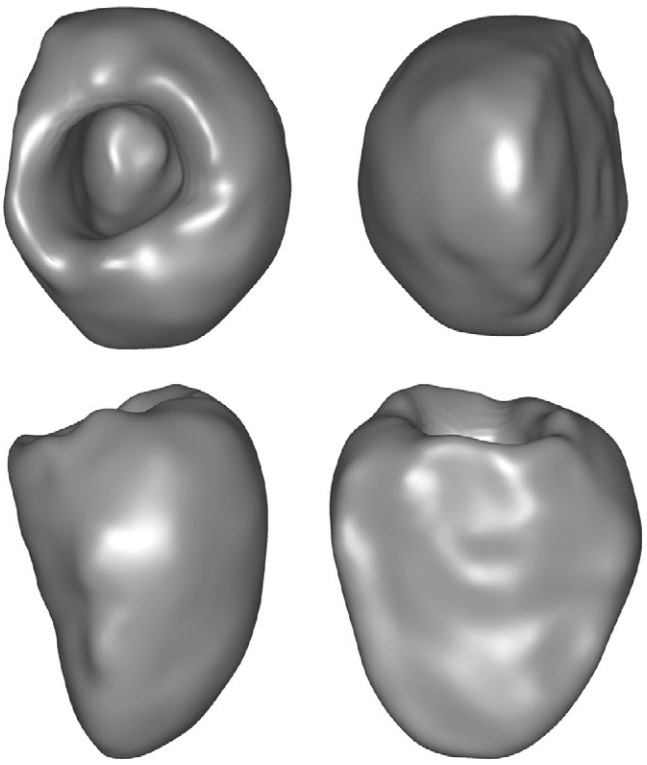

Fig. 1. Geometry of the left ventricle represented as a closed NURB surface (Non-uniform Rational B-Splines) derived from points measured on the epicardial and endocardial surfaces.

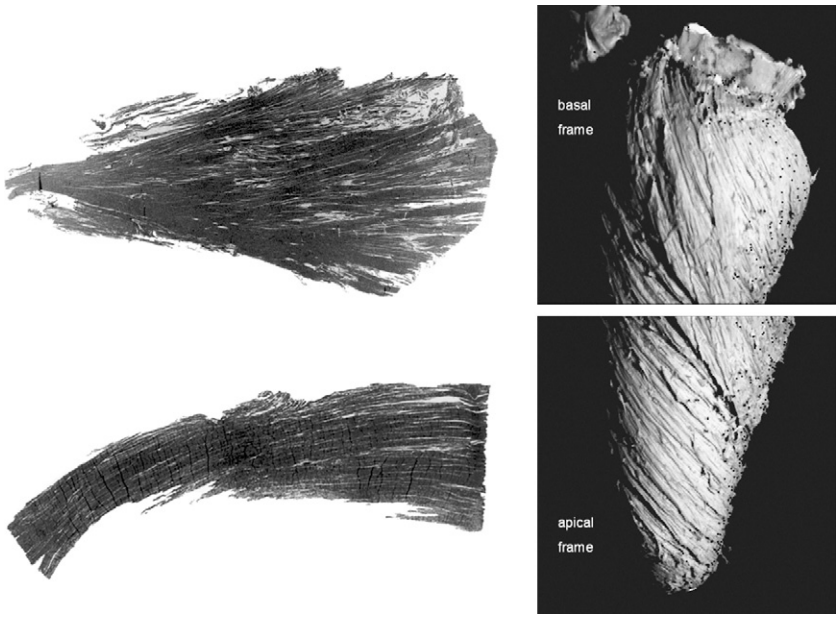

Fig. 2. Left: Histological section through strands of myocardium as they are typically harvested by the peeling procedure. Top: section parallel to the epicardium. Bottom: section with the specimen tilted to radial orientation. Note the prevailing axial alignment parallel to the edges or only slightly deviating from those artefactual surfaces. Right: superior aspect of the left ventricular wall after peeling of the superficial aggregates. After removal of the aggregates, we digitised the resulting grooves.

intact ventricle, and following the global arrangement. To obtain an individual aggregate, one leg of a fine forceps was inserted 1—2 mm deep into the left ventricular wall. The enclosed myocardium was detached from its surroundings and then pulled along its prevailing longitudinal direction, thus sequestering it from its bed. In doing so, we aimed to restrict the strands neither in length nor in their self-organised pathway. Accordingly, minute portions of myocardium were removed sequentially, typically being between 1 and 2 cm in length, 1—2 mm in thickness and up to 4 mm wide (Fig. 2). The process was continued until the entire ventricle was peeled.

While removing the aggregates, it was inevitable that we severed myriads of connections with the neighbouring aggregates, this being a consequence of the ubiquitous branching of the cardiomyocytes. Histological scrutiny, however, confirms that there is a preferred direction prevailing throughout the aggregates (Fig. 2). While the detached aggregates are of limited length (Fig. 2), and variable with respect to their lateral extension, thickness and cross section, the contractile pathways in the ventricular wall in reality have, as mentioned earlier, no beginning and ending, nor do they have natural boundaries towards any side. The peeled strands, therefore, represent no more than the piecewise arrangement of the local main major trajectories of the myocardial structure.

While following the well-defined grooves and crests on the sequentially exposed surfaces with the electromagnetic stylus, we digitised the carved out beds of the aggregates rather than the aggregates themselves (Fig. 2). In this fashion, we obtained a data set that defined the topography and alignment of the housing of the aggregates, which we have taken as surrogates of the contractile pathways within the ventricular wall. A total of some 2700 point sequences were so measured, each sequence representing one recovered aggregate. Care was taken to perform the combined peeling and digitising procedure as fast as possible, keeping evaporation of the specimen to a minimum.

The myocardium was peeled as densely and completely as possible, thereby digitising as many aggregates as possible (Fig. 2). For practical reasons, however, the density of the aggregates which could be recovered varied throughout the

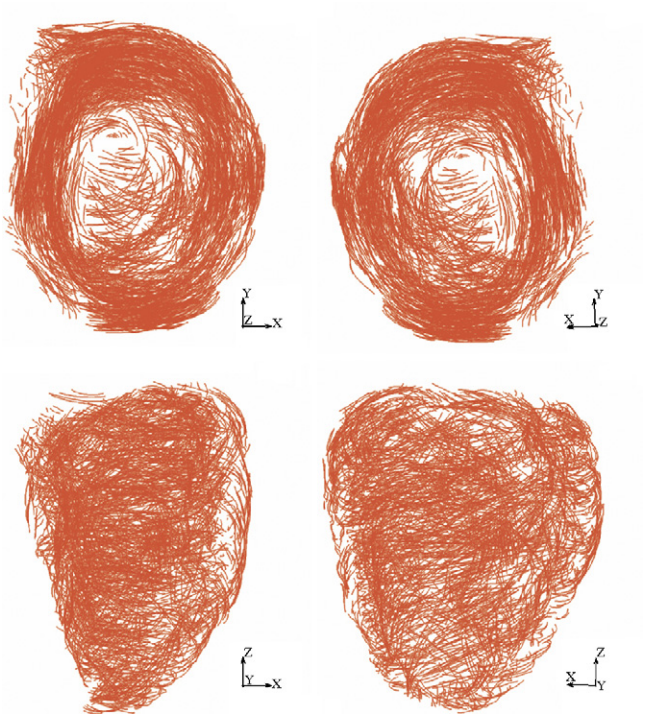

Fig. 3. Measured beds of myocardial aggregates of the left ventricle approximated as cubic splines from the points outlining the grooves which housed the aggregates.

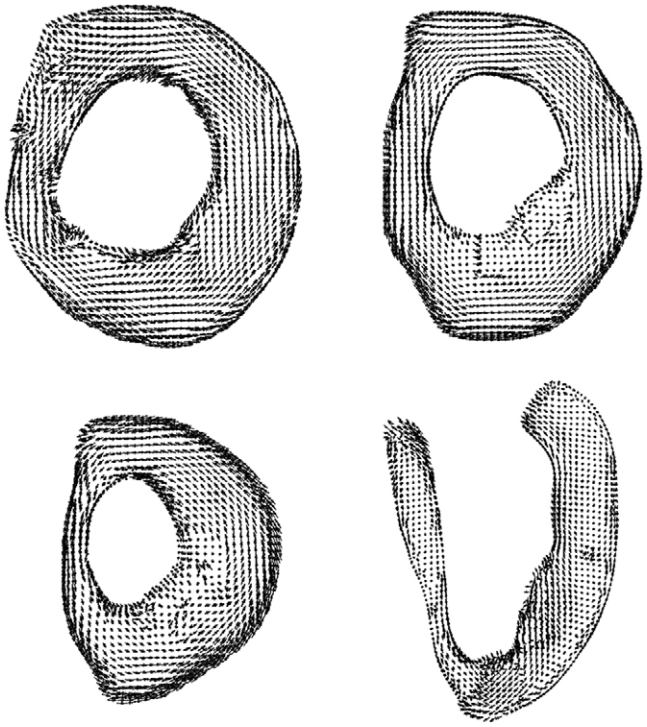

Fig. 4. Anisotropy of the left ventricular wall as reconstructed from digitised myocardial aggregates, and extrapolated as a unit vector field.

ventricular wall. In particular, when approaching the endocardium as well as the apex, less aggregates could be extracted per unit volume without causing disintegration of the remaining tissues.

We then reassembled the pattern of the aggregates removed from the ventricular wall as it was outlined by the closed outer and inner boundaries, respectively. Since the number of aggregates removed per unit volume of tissue was not evenly distributed throughout the myocardium, extrapolation was needed in all cases to complete the pattern (Fig. 3). For this purpose, we applied the mathematical procedure described in the Appendix A, with which the architecture was defined in the form of a uniform field of unit direction vectors (Fig. 4). This field was determined in a systematically selected number of evenly spaced points in the myocardium, whereby the density and arrangement of the points was considered sufficient if it could be used as a finite element mesh (a mesh with more than 47,000 eight-node hexahedral elements was used to include geometrical details of importance).

3. Results

In agreement with previous findings [16], we found the mean helical angle of the aggregates to range from around +85° at the subendocardial surface to −85° at the outer surface (Figs. 4 and 5). We observed considerable local variability of this angle when comparing the subepicardial alignment of the aggregates making up the left ventricular base, midportion and apex, and when comparing the superior, posterior and inferior aspects of the left ventricle.

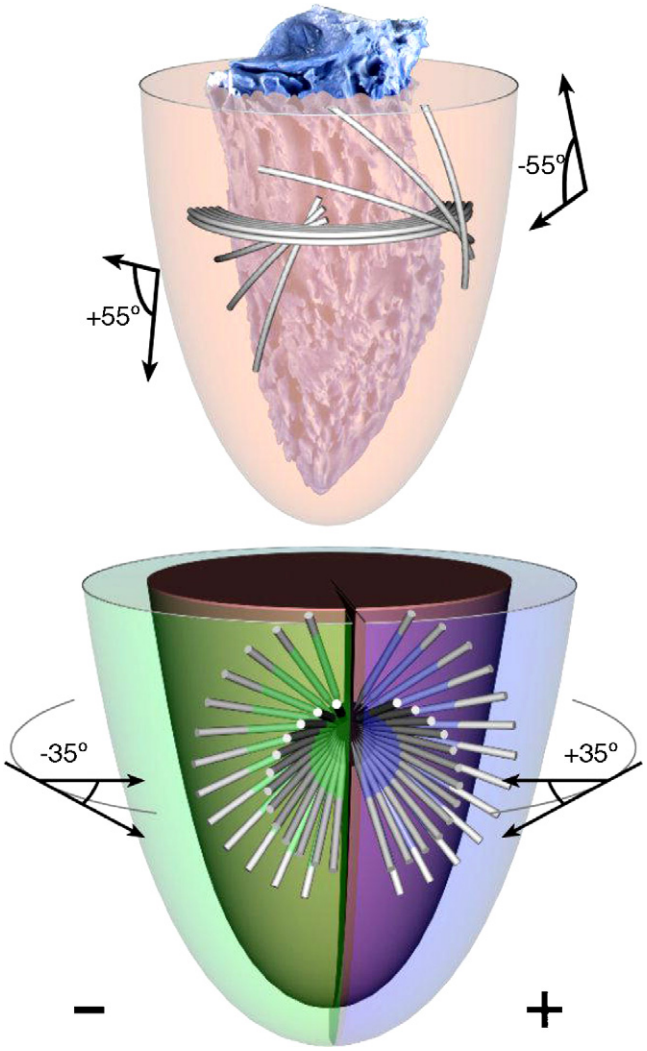

Fig. 5. Top: positive and negative helical angles relative to the equatorial fibres' orientation. Bottom: positive and negative angles of aggregates intruding in epi-endocardial direction.

To assess the angles of intrusion, we used the measured aggregates to create a set of 30 sections through the short axis of the left ventricle, each of about 3 mm thickness, with representative examples shown in Fig. 6. In the apical eight slices, we then found a pronounced concentration of intruding fibres, covering the region extending 2.5 cm from the apex. At the base, the highest number of intruding aggregates was found in the first three slices, which covered the distance of 1 cm from the base, the intruding aggregates being found throughout the circumference of the ventricular wall. Deviations from an essentially tangential alignment were also found in the middle of the ventricle, specifically in slices 3—15, with the largest number of intruding aggregates being located around the obtuse margin. In slices 16—22, in contrast, the aggregates were aligned almost exclusively in tangential fashion. Since the precise tangential orientation cannot be defined in our reconstructed ventricular geometry, we did not consider it justified to attempt to sample quantitatively the differing angles of intrusion. We estimate, nonetheless, that about one-fifth of the aggregates deviate

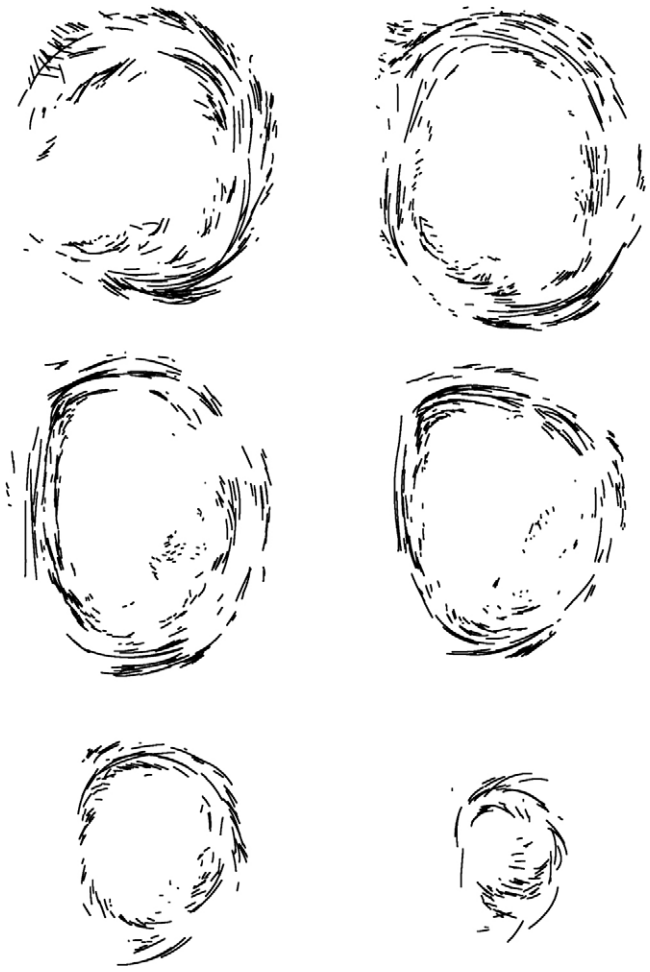

Fig. 6. Projections of measured myocardial aggregates onto selected short axis slices. From 1 through 6, distances are 3 mm, 15 mm, 33 mm, 48 mm, 72 mm and 84 mm, respectively from the base. Although surface-parallel orientations are predominant, a marked local variability is seen in the angle of intrusion. Note also the deformation of the cross-sections, which deviate markedly from a circle.

Fig. 7. Long axis view of the measured myocardial aggregates in selected slices. We have selected six homogeneously distributed slices around the left ventricle.

within a range of up to $\pm 30^{\circ}$ from a hypothetical tangential plane, greater angles being rare and largely artefactual.

Examination of reconstructed longitudinal sections (Fig. 7) revealed significantly greater deviations in the course of the contractile pathways from an estimated alignment parallel to the surface than was seen in the sections reconstructed in the short axis. Comparison between the septum and the free walls revealed more pronounced angles of intrusion in the septum, particularly at the junctions with the free walls. The inferior wall was densely interspersed with short segments oriented obliquely towards the endocardium. Taken overall, our findings show that the myocardium is arranged as a complex three-dimensional and densely interlaced mesh, albeit with no evidence to sustain the notion that there are discrete tracts, bands or ropes within the myocardial mesh.

In terms of cardiodynamics, it has been presumed throughout the 20th century that function is related in strict fashion to individual ventricular geometry [17]. The curvature of radius and the thickness of the ventricular wall, along with left ventricular pressure, are presumed to obey the law of Laplace, this being presumed in turn, albeit in mechanically crude fashion, to determine the shortening of the sarcomeres and the generation of force. Any attempt to determine the radius of mural curvature in the dead heart, however, must be inaccurate, particularly subsequent to fixation. We did not seek, therefore, to make any quantitative evaluation, although we observed that the radius of curvature increased more or less continuously from the ventricular base to the apex.

4. Discussion

The purpose of our present study, albeit of an individual heart, was to provide an authentic display of the myocardial aggregates responsible for contraction of the human left ventricle, seeking to provide an accurate and realistic and exemplary basis for future biomathematical and bioengineering modelling. As with any macroscopic method of dissection applied for the analysis of components extending from macroscopic to submicroscopic levels, the potential of

the procedure is limited by its relatively rough spatial resolution. We hypothesised, nonetheless, that removal of the aggregates of myocytes would leave behind their beds, which would then serve as surrogates of the prevailing structure of the three-dimensional myocytic mesh making up the walls of the left ventricle. The data obtained proved to be sufficiently detailed to permit extrapolation, using mathematical standard procedures, to provide a model which complements the finite element approach to ventricular mechanics and dynamics [18].

The set of digitised data obtained from the examined specimen is special in so far as it represents a configuration of that heart in a further not specified state between its intravital enddiastolic and endsystolic extreme configurations. Furthermore, because of the distending pressure acting on the tissue from the coronary vessels during the postmortem coronary perfusion, the alignment and spatial position of the myocytes forming the aggregates harvested and digitised could be distorted to some extent. Nevertheless, we assume those distending forces to be evenly distributed throughout the ventricular walls so that no major internal remodelling takes place within the myocytic net during the process of fixation apart from the formation of some oedema usually observed in histological studies after fixation by perfusion

Our reconstruction of the individual human heart confirms previous studies, showing that the outer and the endocardial components of the ventricular walls are made up primarily of aggregates aligned essentially tangentially to a virtual surface plane. We also confirmed that the helical angle of the subendocardial zones, as seen from the base, increase markedly in an anticlockwise fashion when traced from the apex to the base, while the angles of the subepicardial aggregates ascend in a clockwise fashion [5,19]. In the midportion of the ventricular wall, and in particular adjacent to the ventricular base, the myocardial cells are oriented in a circular fashion, forming the 'triebwerkzeug'. This finding has also subsequently been confirmed by several investigators [5,20,21].

The overall arrangement demonstrated by our reconstruction is that of a myocardial mesh, produced by countless lateral off-springs and lateral connections with adjacent aggregates, such that the orientation of the longitudinal axis of the elongated myocytic aggregates spans a cone around the main axis of anisotropy. The opening angle of this cone is around 10°, albeit that this varies locally. Because of the abundant small planes of cleavage, the cones themselves are not axisymmetric. The deviation we observed from a strictly tangential alignment, nonetheless, is far greater than was recognised by Streeter [19]. Meanwhile, we have confirmed the prevalence of the pronounced angulation of the epi-endocardially intruding component of the myocardial net by histology using a semi-circular section technique [22] and by magnetic resonance diffusion tensor imaging (submitted). Functional interpretation of these findings is far from straightforward [23]. Standard histological images show no more than the prevailing axial orientation of a population of aggregated myocardial cells. It is generally assumed that this visualised axis is the surrogate of the main direction of force engendered by the myocytes producing the image. In combination with the collageneous network, however, the frequent collateral linkages between the myocytes intercept the transmission of contractile forces, spreading them away from the primary orientation of the myocardial aggregates [23]. Because of this, the axes measured in histologic or macroscopic preparations must be expected to deviate not only from the direction of movement of the myocardial aggregates during systolic shortening, but also from the principal direction of stress.

There is no doubt about the prevalence of marked heterogeneity in the arrangement of the myocytic aggregates making up the left ventricular walls. These heterogeneities unequivocally produce a helical pattern when looking down on the basal surface of the walls. There is no evidence, however, to show that these helical elements are part of a system of tracts or bands that can be traced in a uniform fashion from the aorta to the pulmonary trunk. There are, however, ubiquitous heterogeneities within the mesh throughout the ventricular walls, not only within the left ventricle but also within the right ventricle, which was not studied in our investigation. It is our opinion that these heterogeneities aid in self-stabilisation of the ventricular wall so as to provide optimal overall systolic contraction and relaxation [22,23].

The largest number of contractile pathways deviating from a parallel alignment with the epicardial surface was found at the apex. This particular arrangement, also appearing as a helix when viewed from the apex subsequent to removal of the epicardium, has been associated with the cyclic twisting of the apex. Its functional significance may be of secondary, since Stuber et al. [24] and other investigators have argued that, particularly in the hypertrophied heart, both apical twisting and its reversal are essentially confined to the period of ventricular ejection. More importantly, recent surgical methods of ventricular reshaping, such as partial left ventriculectomy [25], have shown that a complete inactivation, and even resection, of the apical spiral compartment are compatible with an important improvement in function of the previously failing heart.

In summary, the accurate model we have prepared showing the architecture of the myocardial aggregates in the left ventricle of one human heart emphasises its asymmetrical and locally inhomogeneous structure, while revealing a global wellorganised anisotropic architecture. Of the several demonstrated features that received less attention in previous models [13,14], the most important is the marked intrusion of the aggregates with respect to outer and endocardial surfaces. Likewise, it is important to note that our reconstruction provides no evidence which would support the notion of an anatomic or functional compartmentation of the myocardium in the form of, e.g., a helical band.

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Appendix A. Determination of a unit vector field describing the architecture of the myocardial aggregates

The approximately 2700 point sequences which were obtained from the peeling and digitising process contained up to 20 individual points. In each sequence, four points on both ends were discarded, because these points were often inaccurate due to the manual peeling procedure which was particularly critical during approaching and removing the stylus at the endpoints. Accordingly, we omitted sequences consisting of less than 12 points. The trajectories were smoothed and converted into cubic splines [NAG, Oxford] (Fig. 3). Depending on the length of the segment, at least 4, and at most 90, regularly spaced new points were interpolated on each spline and utilised to represent a trajectory.

The mesh generator of the software system MSC Marc-Mentat® was used to subdivide the volume given by the closed epicardial and endocardial surfaces. A hexahedral mesh consisting of about 47,000 nodes resulted, whose coordinates were defined in a global rectangular Cartesian coordinate system. The 47,000 elements contained around 70,000 points on the trajectories of aggregates.

Next, the unit vector field was calculated. Given two interpolated points, P_i and P_{i+1}, with the position vectors (bold characters are used to denote vectors) $\mathbf{r}_F(P_i)$ and $\mathbf{r}_F(P_{i+1})$ on an arbitrary trajectory F, the middle point Z_i is

$$\mathbf{r}_F(Z_i) = \tfrac{1}{2}\{\mathbf{r}_F(P_i) + \mathbf{r}_F(P_{i+1})\}$$

These consecutive points, P_i and P_{i+1}, define a direction vector,

$$\mathbf{v}_F(Z_i) = \mathbf{r}_F(P_{i+1}) - \mathbf{r}_F(P_i)$$

Since the points on the trajectory were chosen sufficiently close together, and since the trajectory is a smooth curve, we were able to use this vector as an approximation for the tangent vector at the middle point of the arc between the two points.

For each hexahedral element, E_j, obtained from the meshing procedure mentioned above, an interior point M_j was defined whose coordinates were given as the average value of the coordinates of the eight corner nodes. A spherical neighbourhood of radius R around M_j was chosen and the distance $d(Z_i,M_j)$ between all points Z_i on the arbitrary trajectory F and M_j was calculated. In case that $R \succ d$, the point Z_i was within the sphere; if the next point, i.e., Z_{i+1} was within the sphere too, we concluded that the vector $\mathbf{v}_F(Z_i)$ was likewise within the sphere. This procedure was repeated for all trajectories and for all of their points Z_i to find the number of curves which cross the sphere.

The radius R had to be estimated suitably at the beginning; if the number of curves crossing the sphere was zero or too small, R was increased and the procedure repeated until there were at least three curves in the chosen sphere around point M_j. From all direction vectors $\mathbf{v}_F(Z_i)$ which were inside the spherical neighbourhood of M_j, an average aggregate direction vector for the element E_j was determined with the aid of a weighting function W_i. Thereby, the vectors which were closer to the centre of the element obtained a heavier weight than more remote ones, such that

$$\mathbf{v}_{\text{average}}(E_j) = \sum_i W_i \mathbf{v}_F(Z_i)$$

Upon normalisation we obtained

$$\mathbf{N}(E_j) = \frac{\mathbf{v}_{\text{average}}(E_j)}{|\mathbf{v}_{\text{average}}(E_j)|}$$

As an approximation for the weighting function W we used the form

$$W_i = \frac{1}{\{c_t(d_t)^n + c_n(d_n)^m\}^p}$$

where the values of the constant parameters are chosen as follows

$c_t = 0.1$
$c_n = 1$
$n = 2$
$m = 2$
$p = 1.5$

and

$$d(Z_i, M_j) = \sqrt{(d_t)^2 + (d_n)^2}$$

Here, d_t and d_n are the tangential and normal distances of M_j and Z_i, respectively.

It is important to note at this point that even though the particular choice of the constant parameters can change, the weighting function W_i and as a

result the defined average anisotropy direction in E_j element, these variations are much smaller than the average deviations of $\mathbf{v}_F(Z_i)$ with respect to $\mathbf{v}_{\text{average}}(E_j)$, so that the general pattern of orientation of aggregates will not change remarkably.

Finally, we reconstructed a uniform field of unit vectors from the digitised trajectories of aggregates that described the architecture (Fig. 4). Based on this field, we were able to make a statistical evaluation of the interpolated orientation of the myocardial aggregates. We calculated the average of the $\mathbf{v}_F(Z_i)$ vectors in all Z_i points inside a spherical neighborhood of M_j, and denoted it as the aggregate direction vector of the element E_j.

The question arises with respect to the size of the discretisation which introduces some uncertainties. From a cardiodynamics' point of view, it was demonstrated that this uncertainty has no major impact on the systolic deformation pattern using a finite element simulation [13], accordingly, a higher resolution of the spatial discretisation is not necessary for this purpose. In our sample, most of the elements (more than 95%) included between 3 and 15 trajectories for the chosen radius R = 5 mm of the spherical neighbourhood. It means that in most locations of myocardium, the attributed average anisotropy direction is determined by averaging of 3—15 measured trajectories in a spherical neighbourhood of 5 mm.